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Malignant Lymphomas: Cell Surface Markers and Advances in Classification

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Identification of cell surface markers permits detailed analysis and classification of the cells involved in the immune response. Application of these techniques to the study of malignant lymphomas has led to our understanding of these tumors as neoplasms of specific elements of the immune system. This approach, which emphasizes functional characteristics of the neoplastic cells, promises to revolutionize the diagnosis and classification of the lymphomas and replace classifications based solely on morphology.

THE PAST DECADE has witnessed a rapid growth of interest and research in malignant lymphomas. This has been stimulated both by the recognition of the therapeutic responsiveness of some of these tumors and by the explosive growth of information in immunology and the emergence of cellular immunology as a discipline. The development of cell surface markers has permitted the recognition and identification of specific physiological classes of lymphoid cells involved in the immune response. Application of these techniques to the study of the malignant lymphomas has led to our current understanding of these tumors as neoplastic proliferations of specific elements of the immune system. This approach now promises a rational classification of the lymphomas, which will supplant confusing and misleading classifications based solely on morphology. This review will consider the markers currently in use, our present understanding of the ontogeny of the immune system and the classification of specific lymphomas as neoplasms of elements of the immune system. The current histopathologic classifications will also be considered.

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Markers and Ontogeny of the Immune System

The major physiological classes of lymphoid cells are distinguished by a variety of cell surface markers.[1] These appear on lymphoid cells in a characteristic sequence accompanying cellular differentiation and relate to immune cell function. Identification of markers on a cell (cell "phenotyping"), therefore, may indicate the physiological class of the cell (for example, B, T or true histiocytic) as well as its stage of development (Figure 1). As applied to lymphomas, this type of information permits classification of the lymphoma as to cell of origin as well as information as to the level at which neoplastic differentiation has been "blocked."[2] The marker sequences for the major cell classes are distinct and will be discussed separately.

B Cells

Circulating mature B cells carry a variety of readily detectable markers: surface immunoglob-

ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
C′ = complement
CIg = cytoplasmic immunoglobulin
CLL = chronic lymphocytic leukemia
SIg = surface immunoglobulin
TdT = terminal deoxynucleotidyl transferase
WDLL = well-differentiated lymphocytic lymphoma

ulin (SIg), Ia-like antigens, and receptors for complement and for the Fc portion of IgG.[3,4] Surface immunoglobulin is most readily detectable by immunofluorescence with heterologous antisera to the major classes of human immunoglobulins: IgA, G, D, M and the light chains *k* and λ. Nonspecific binding of antibody to Fc receptors may be circumvented by using Fab fragments rather than whole antibody. Receptors for complement (C′) are detected by a rosette reaction using sheep erythrocytes sensitized with antibody (IgM) and complement, so-called EAC rosettes. The sensitized antibody-complement coated erythrocytes will bind specifically to lymphocytes expressing receptors for complement. Fc receptors are detected by a similar rosetting reaction using erythrocytes sensitized only with antibody (IgG), so-called EA rosettes. The antibody coated erythrocytes bind specifically to lymphocytes expressing receptors for the Fc portion of IgG.

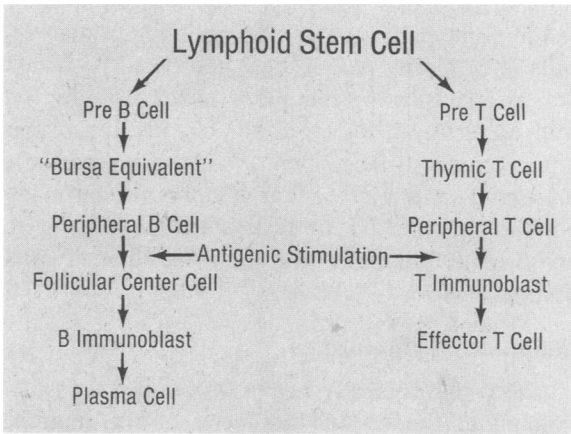

Figure 1.—Ontogeny of the cellular immune system.

TABLE 1.—*Markers of Developing Lymphoid Cells*

	CIg	*SIg*	*C′*	*TdT*	*E rosette*
Stem cell	−	−	−	?	−
Pre-T cell	−	−	−	+	−
Thymic T cell	−	−	−	+	+
Peripheral T cell	−	−	−	−	+
T immunoblast	−	−	−	−	+
Pre-B cell	+	−	−	+	−
Peripheral B cell	−	+	+	−	−
B immunoblast	+	+	+	−	−
Plasma cell	+	−	−	−	−

C′ = receptor for complement; CIg = cytoplasmic immunoglobulin; E rosette = receptor for sheep erythrocytes; SIg = surface immunoglobulin; TdT = terminal deoxynucleotidyl transferase

The earliest identifiable B cell precursor in the bone marrow is the pre-B cell (Table 1). These morphologically lymphoblast-like cells lack the specific B cell markers noted above but demonstrate a small amount of intracytoplasmic IgM (CIg).[5] With further maturation, CIg disappears as SIg makes its appearance. Receptors for the components of complement also appear in sequence during B cell maturation.[6] With antigenic stimulation, B cells undergo a proliferative response. The region of B cell proliferation in the lymph node is the follicular center or germinal center. In these regions, Lukes and Collins[7] have described a characteristic morphological transformation of the small lymphocyte through stages of small and large cleaved cell, small and large noncleaved cell and B immunoblast. The cleaved morphology consisting of a clefted or indented nucleus is thought to be characteristic of follicular center B lymphocytes. The follicular B lymphocyte also demonstrates increased SIg and C′ receptors. The immunoblast or fully transformed B cell is considered to be the immediate precursor of the plasma cell, the antibody-secreting effector cell of the B cell lineage. At the immunoblastic stage of transformation, cytoplasmic immunoglobulin again makes its appearance. With terminal plasma cell differentiation, the B cell surface markers (SIg, Ia, C′ and Fc) are lost and cytoplasmic immunoglobulin predominates.

T Cells

The major surface marker of the mature T cell is a receptor for sheep erythrocytes, the so-called E rosette reaction. The nature of the receptor and its binding site on the sheep erythrocyte is not understood. T cells are also recognized by reactions with specific alloantisera or monoclonal antibodies.[8] Certain T cell classes also possess receptors for IgG and IgM Fc portions. The earliest recognizable T cell precursor in the marrow is the pre-T cell (Table 1). This cell lacks receptors for sheep erythrocytes but reacts with certain anti-T antisera. The pre-T cell also contains a peculiar DNA synthetic enzyme, terminal deoxy-

nucleotidyl transferase (TdT).[9,10] This enzyme has the characteristic property of adding bases nonspecifically to a DNA terminus. It is, therefore, unlike the usual DNA polymerases, which are template dependent.

It has been postulated that TdT may function as a somatic mutagen and play a role in the generation of immunologic diversity.[11] Although originally thought to be a marker for T cell precursors, TdT has since been recognized in pre-B cells as well and may be a marker for certain classes of lymphoid stem cell.[5,12] Normal TdT activity in the marrow is thought to be due to the presence of these cells. Pre-T cells from the marrow migrate to the thymus where they differentiate under the influence of the thymic epithelium. Thymic T cells possess both receptors for sheep erythrocytes and TdT, which accounts for the high level of TdT found in this organ.[12] Mature circulating T cells retain receptors for sheep erythrocytes, but TdT activity is lost. Curiously, although immunoblast transformation occurs with antigenic or mitogen stimulation, TdT activity is not regained. The T immunoblast or transformed T cell is the precursor of T effector cells, which mediate delayed hypersensitivity. The atypical or reactive lymphocytes, which circulate in viral or hypersensitivity illnesses, are closely related to immunoblasts of T and B origin.[13] Certain classes of T cells exhibit a characteristic morphology described as convoluted or cerebriform.[7] These terms refer to elaborate nuclear infoldings resembling the cerebral gyri and sulci. This morphology is associated with some neoplastic T lymphoblasts[14] and with T lymphocytes in the skin, particularly those associated with mycosis fungoides and Sézary syndrome.[15]

Macrophages or "True" Histiocytes

Much confusion has arisen from the uncritical use of the term "histiocyte" in morphological pathology for any large lymphoreticular cell. Properly speaking, the macrophage or true histiocyte is a phagocytic cell derived from circulating blood monocytes and, ultimately, from the bone marrow.[16] The marrow origin of monocytes and tissue histiocytes has been established by both marrow culture and marrow transplantation experiments.

Histiocytes (and their precursors, monocytes) possess Ia-like antigens and receptors for complement and Fc.[17] They lack endogenous surface immunoglobulin (but may acquire exogenous immunoglobulin by virtue of avid Fc receptors). Histiocytes are rich in acid hydrolases, particularly lysozyme or muramidase.[18] Immunoperoxidase staining for muramidase has been used as a specific marker. Phagocytosis of latex particles or sensitized erythrocytes has also been used as a histiocytic marker.

Homing and Lymphocyte Domains

Early marker experiments showed that the distribution of lymphocyte types within a lymph node is not random, but that specific domains exist. B cells are distributed predominantly in the cortical follicles and medullary cords of lymph nodes and in the follicles or white pulp of the spleen. T cells are predominantly distributed in the paracortical or interfollicular region of lymph nodes and in the periarteriolar sheaths of the spleen. Histiocytes are distributed in the marginal and medullary sinuses of the lymph node and in the red pulp sinuses of the spleen. These data are confirmed by "experiments of nature"—that is, the immunodeficiency disorders: B cell immunodeficiency (Bruton-type agammaglobulinemia) results in primarily follicular depletion whereas T cell immunodeficiency (DiGeorge's syndrome) results in primarily paracortical depletion. Although the mechanisms of lymphocyte homing are not well understood, they presumably involve recognition of cell surface signals.[19] These are partially preserved in the malignant lymphomas as many lymphomas of B, T or histiocytic origin tend to involve preferentially the corresponding lymph node domain.[20]

Malignant Lymphomas

Given the presently available detailed information about the normal ontogeny of the immune system, it is possible to consider the malignant lymphomas as neoplastic proliferations of specific elements of the immune system whose differentiation has been "blocked" at certain levels of development (Table 2). This approach to classification will likely supplant those based purely on morphological description. However, because of the vast volume of clinicopathologic correlation related to the morphological classifications, these approaches are still clinically useful and necessary. The original classification of the malignant lymphomas evolved during the first half of this century and recognized three categories of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma. In modern terms, these

roughly correspond to lymphocytic or small cell lymphoma, histiocytic or large cell lymphoma and nodular lymphoma. This classification has subsequently been expanded in the two modern American classifications: that of Rappaport[21] and that of Lukes-Collins.[22a] The Rappaport classification (Table 3) was proposed as a purely descriptive approach and has served well clinically, although we now know several of the terms and concepts are biologically incorrect. The Lukes-Collins classification (Table 4) is newer and proposes a functional or immunologic classification.[22b,22c] Recently, a National Cancer Institute-sponsored study has led to a new working formulation of the non-Hodgkin's lymphomas (Table 5).[23] The formulation is based on prognostic divisions among the lymphomas and uses a nomenclature which although descriptive is biologically correct. It is hoped that the formulation, which facilitates a translation of terminology among the major classifications, will permit a greater degree of comparability among clinical studies. In discussing some of the specific malignant lymphomas, I will attempt to give the classification in each of the two major American systems and the proposed formulation.

TABLE 2.—*Lymphomas as Neoplasms of Specific Cell Classes of the Immune System*

B Cell	
Pre-B cell	ALL (rare)
Medullary B cell	CLL
	Small lymphocytic lymphoma
Follicular B cell	Follicular lymphomas
	Large cell lymphoma
	Burkitt's lymphoma
B Immunoblast	Large cell lymphoma
T Cell	
Pre-T cell	ALL (common)
Thymic T cell	ALL (uncommon)
	Lymphoblastic lymphoma
T cell	CLL (rare)
	Sézary—mycosis fungoides
T immunoblast	Large cell lymphoma (rare)
Histiocytic	
Histiocyte	Malignant histiocytosis
	Hodgkin's disease (?)

ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia.

TABLE 3.—*Non-Hodgkin's Lymphoma: Rappaport Classification (1966)**

Nodular or diffuse
- Undifferentiated
- Lymphocytic lymphoma, well-differentiated
- Lymphocytic lymphoma, poorly differentiated
- Mixed lymphocytic—histiocytic
- Histiocytic lymphoma

*From Rappaport.[21]

TABLE 4.—*Non-Hodgkin's Lymphoma: Lukes-Collins Classification**

U cell (undefined)	
T cell	B cell
Small lymphocyte	Small lymphocyte
Convoluted lymphocyte	Plasmacytoid lymphocyte
Cerebriform cell of Sézary's syndrome and mycosis fungoides	Follicular center cell types (Follicular, follicular and diffuse, diffuse)
	Small cleaved
Lymphoepithelioid cell	Large cleaved
	Small noncleaved
	Large noncleaved
Immunoblastic sarcoma	Immunoblastic sarcoma
Histiocytic	

*From Lukes.[22c]

TABLE 5.—*Non-Hodgkin's Lymphoma: A Working Formulation for Clinical Usage**

Low grade
- Small lymphocytic
- Follicular, small cleaved cell
- Follicular, mixed small cleaved and large cell

Intermediate grade
- Follicular, large cell
- Diffuse, small cleaved cell
- Diffuse, mixed small cleaved and large cell
- Diffuse, large cell—cleaved and noncleaved

High grade
- Diffuse, large cell—immunoblastic
- Small noncleaved cell (Burkitt and non-Burkitt)
- Lymphoblastic (convoluted and nonconvoluted)

*From Berard.[23]

Malignant Lymphomas of B Cell Origin

Small Lymphocytic Lymphomas

[*Well-differentiated lymphocytic lymphoma (Rappaport). Small lymphocytic lymphoma (Lukes-Collins). Low-grade lymphoma, small lymphocytic (Working Formulation).*]

These are lymphomas composed of small round lymphocytes morphologically resembling the small peripheral blood lymphocyte. The morphology is indistinguishable from that of chronic lymphocytic leukemia (CLL) of which it appears to represent the tissue phase. Waldenström's macroglobulinemia and the heavy chain diseases are closely related lymphomas demonstrating plasmacytoid features.[24]

Well-differentiated lymphocytic lymphoma (WDLL) and CLL are almost always B cell neoplasms.[25] Rare instances of T cell CLL have been described and represent a distinct clinical entity, with a high incidence of skin and central nervous

system involvement.[26] In these cases the cells are mature T cells with positive E rosettes and absent TdT.

The much more common B cell cases demonstrate surface immunoglobulin (IgM or IgM + IgD) and receptors for complement.[27] The SIg is restricted to a single light chain class, *k* or λ, indicating the monoclonal nature of the proliferation. This feature may be diagnostically useful occasionally in distinguishing a reactive lymphocytic proliferation, which does not show light chain restriction. Recent data have suggested a similar restriction of complement receptor expression, the majority of cases showing only receptors for C 3 d.[6] The marker pattern of cells from WDLL is identical to that of CLL, which indicates the fundamental relatedness of the two conditions.[27] B cells from either CLL or WDLL demonstrate a low-density pattern of SIg staining and a weak receptor for complement. Studies of normal lymph nodes demonstrate that these are the features of medullary B lymphocytes, suggesting that both CLL and WDLL arise from the small medullary lymphocyte.[2] This is consistent with the histological observation that WDLL is always a diffuse process unrelated to follicular centers. Occasionally CLL or WDLL may terminate in a rapidly progressive large cell lymphoma (so-called Richter's syndrome). In the cases examined, the surface markers and light chain restriction are retained, which suggests this phenomenon is a result of clonal evolution.[28] Lymphocytic lymphoma of so-called intermediate differentiation is a closely related entity that appears to arise from the small lymphocytes of the perifollicular cuff.[29]

Nodular Lymphomas

[*Nodular poorly differentiated lymphocytic, nodular mixed, nodular histiocytic (Rappaport). Follicular center cell lymphoma, small cleaved, large cleaved, large noncleaved (Lukes-Collins). Low-grade lymphoma, follicular, small cleaved cell, mixed small cleaved and large cell; intermediate-grade lymphoma, follicular, large cell (Working Formulation).*]

The relatively good prognosis of lymphomas with a nodular pattern was recognized early in this century, with a serious debate as to whether "giant follicular lymphoblastoma" was actually a malignant disease. Although Rappaport introduced the term nodular lymphoma as a purely descriptive term, it is now appreciated that these tumors arise from and attempt to recapitulate the cells of the lymph node follicle.[3] The term follicular lymphoma is therefore more apt. The bewildering array of cytologic features observed in these tumors is now appreciated to reflect the cytologic pleomorphism of the follicular center.

Marker studies of nodular lymphomas demonstrate them invariably to be composed of monoclonal B cells.[3,30] The cells possess a high-density pattern of SIg (IgM or IgM + D) and a strong complement receptor. These are the features of the normal follicular center cell, which supports the concept of nodular lymphomas as neoplasms of follicular lymphocytes.[3]

Cystologically, the hallmark of follicular lymphocytes is the cleaved cell.[7] The cleaved cell is a small or large lymphoid cell that has a deep nuclear cleft resulting in an irregular or peanut configuration. These are the cells identified by hematologists in so-called lymphosarcoma cell leukemia as "buttock" cells. Rappaport originally considered these cells poorly differentiated lymphocytes—hence, the term poorly differentiated lymphocytic lymphoma. We now appreciate that these cells are in reality well-differentiated follicular center cells.[31] The cytologic diversity of follicular lymphomas corresponds to the cytologic pleomorphism of the follicular center. The morphogenesis of follicular center cells has been elaborately described by Lukes and Collins.[7] Follicular lymphomas are classified according to the dominant cell type: small cleaved, mixed small cleaved and large cell, or large cell (Working Formulation). The biological aggressiveness appears to relate directly to the component of mitotically active large cells. Occasionally, lymphomas are observed with a diffuse pattern but composed of follicular-type cleaved cells, so-called diffuse poorly differentiated lymphocytic lymphoma (Rappaport) or intermediate-grade lymphoma, diffuse small cleaved cell (Working Formulation). These appear to represent follicular cell lymphomas that have lost the ability to form recognizable follicles and have a correspondingly worse prognosis.

Burkitt's Lymphoma

[*Undifferentiated lymphoma, Burkitt's type (Rappaport). Follicular center cell lymphoma, small noncleaved (Lukes-Collins). High-grade lymphoma, small noncleaved cell (Working Formulation).*]

Burkitt's lymphoma is a neoplasm originally identified in African children by Sir Dennis Burkitt.[32] Subsequently, cases with identical histology

have been identified in the United States.[33] Cases of Burkitt's lymphoma in the United States appear to differ from the African form of the disease in that the association with Epstein-Barr virus is much less strong, and the classic jaw tumors are seldom seen. The poorer therapeutic response of the American cases of the disease has been attributed to the higher incidence of advanced abdominal presentations.[34]

Histologically, Burkitt's lymphoma is characterized by a diffuse proliferation of mitotically very active "undifferentiated" lymphoid cells interspersed with benign phagocytic histiocytes that produce the so-called starry sky appearance. The results of immunologic marker studies suggest that the cells are not undifferentiated or stem cells as originally suggested, but are rapidly proliferating B cells.[35] In this series[35] of American cases, all eight demonstrated high-density staining for surface immunoglobulin (IgM) and a variable number of cells with receptors for complement. Lukes and Collins have suggested that the Burkitt cell is morphologically similar to a cell of the follicular center—the small noncleaved follicular center cell.[7] This suggestion is supported by the observation that early Burkitt's lymphoma may show a partially follicular pattern, with selective involvement of follicular centers.[2] Thus, Burkitt's lymphoma may be the childhood equivalent of the much more common follicular center cell lymphomas of adults.

Large Cell Lymphomas

[*Large cell or histiocytic lymphoma (Rappaport). Follicular center cell lymphoma, large cleaved and large noncleaved; immunoblastic sarcoma of B cells (Lukes-Collins). Intermediate grade lymphoma, large cell, cleaved or noncleaved; high-grade lymphoma, immunoblastic (Working Formulation).*]

The large cell lymphomas are immunologically heterogeneous, but in most series the majority (50 percent to 60 percent) appear to arise from B cells.[2] The term histiocytic lymphoma, synonymous with large cell lymphoma, is a misnomer stemming from the uncritical use of the term histiocyte for any large lymphoreticular cell. The overwhelming majority of large cell lymphomas arise from transformed lymphoid cells, with only rare examples possessing true histiocytic markers. In a series of 19 cases studied at the National Cancer Institute, 11 had B cell markers (SIg 10 C′ 9), 2 had T cell markers (E rosettes), 1 had true histiocytic markers (C′, esterase and phagocytosis) and 5 had no detectable markers (null cells).[2] Thus, the large cell histology appears to be a final common pathway for highly malignant tumors of all arms of the immune system, but most commonly B cell.

Morphological subclassification of large cell lymphomas is controversial, but it appears that subgroups can be recognized histologically. Lukes[7] divided the large cell lymphomas into follicular center types, which showed evidence of follicular center cell differentiation (large cleaved and large noncleaved) and immunoblastic types, which showed large transformed lymphoid cells with intensely pyroninophilic cytoplasm and plasmacytoid features. In a review of cases at the National Cancer Institute, the prognosis for large cell lymphomas with follicular center differentiation (large cleaved, large noncleaved and mixed follicular center cell) was superior to lymphomas without follicular center differentiation (so-called pleomorphic pyroninophilic and blastic).[36] Thus, the large cell lymphomas can be divided into at least two prognostically significant groups, the follicular center cell type and the immunoblastic type. This division has been incorporated into the working formulation.

Large cell lymphomas of non-B cell origin are difficult to recognize morphologically. Large cell lymphomas of true histiocytic origin are closely related to malignant histiocytosis *(vide infra)* of which they probably represent a tumoral phase. Occasional large cell lymphomas of T cell origin can be recognized by the presence of large cells with convoluted nuclei.[37] A recent study suggests that the presence of B or T markers may be of prognostic significance.[38]

Malignant Lymphomas of T Cell Origin

Lymphoblastic Lymphoma

[*Lymphoblastic lymphoma (Rappaport). Convoluted lymphocytic lymphoma (Lukes-Collins). High-grade lymphoma, lymphoblastic (Working Formulation).*]

Lymphoblastic lymphoma is closely related to the more familiar acute lymphoblastic leukemia (ALL).[14] Recent immunologic data suggest that ALL arises from classes of lymphoid stem cells (pre-B, pre-T, and thymic T) and that lymphoblastic lymphoma represents the tissue phase of T cell ALL.[39,40] Lymphoblastic lymphoma affects primarily adolescent boys with a high incidence thymic mass and leukemic transformation. The

histology of lymphoblastic lymphoma is identical to that of ALL in lymph nodes. The occurrence of so-called convoluted cells in this disorder has received much attention.[14] This refers to complex nuclear foldings seen in a variable proportion of both lymphoblastic lymphoma and ALL. The presence of convoluted cells is of diagnostic value but not of any special prognostic significance.[14]

Results of cell marker studies in lymphoblastic lymphoma demonstrate the features of immature thymic-type T cells.[41] More than half the cases form E rosettes, and TdT is almost invariably present.[42] This is identical to the findings in T cell ALL but is in contrast to the more common null cell ALL which is TdT-positive but does not form E rosettes. The hypothesis that lymphoblastic lymphoma is of T cell origin is supported by the selective involvement of T cell domains, including the thymus and paracortical regions of lymph nodes.

Sézary Syndrome—Mycosis Fungoides

Mycosis fungoides is a progressive skin disorder, now recognized to be a malignant lymphoma with selective skin involvement. The Sézary syndrome is a closely related condition with circulating abnormal cells, and may be considered the leukemic phase of mycosis fungoides. Although the older literature is replete with reports of Hodgkin's disease and other lymphomas developing in patients with mycosis, it is now apparent that these represent terminal visceral spread of mycosis fungoides.[43]

The Sézary-mycosis cell has a unique morphology described as cerebriform.[15] The nucleus is infolded with extreme complexity, best appreciated in plastic-embedded thin sections. This morphology may be characteristic of the skin lymphocyte, as similar cells may be seen in benign inflammatory conditions of the skin.[44] Marker studies have shown that the Sézary-mycosis cell is a mature T cell (E rosette-positive, TdT-negative), and in some cases the cells have in vitro helper T cell function.[45,46] The cells are peculiarly epidermotrophic with a propensity for infiltrating the epidermis as single cells or groups (so-called Pautrier microabscesses).[47] The special clinicopathologic features of mycosis fungoides are a direct result of this epidermotrophism. Mycosis fungoides characteristically progresses from an inflammatory premycotic phase, through a plaque phase to a tumor phase. In the early stages of the disease, regional lymph nodes show the changes of dermatopathic lymphadenitis, consisting of histiocytic hyperplasia and melanin deposition. With advanced disease, paracortical (T zone) infiltration with mycosis cells occurs and, ultimately, visceral involvement as well.[43] While still confined to the skin, treatment with electron beam may result in prolonged remission. The diagnosis of mycosis fungoides may be very difficult to confirm in the early premycotic stage as the histological findings are nonspecific. Parapsoriasis en plaque and follicular mucinosis may precede the development of mycosis fungoides. When characteristic Pautrier microabscesses (group infiltration of the epidermis by Sézary-mycosis cells) are identified, the diagnosis becomes more certain. Lymphomatoid papulosis, a benign self-limited condition may closely mimic the histological findings in mycosis fungoides.[48] The diagnosis of Sézary syndrome is based on the identification of circulating abnormal lymphoid cells, usually found in a patient with diffuse erythroderma. The Sézary cells as seen in the peripheral blood show complex nuclear folding and periodic acid Shiff-positive vacuolization. Caution must be exercised, however, as small numbers of similar cells may be seen in patients with extensive benign inflammatory dermatoses.[44]

Malignant Lymphomas of True Histiocytic Origin

As noted previously, "histiocytic" lymphoma is usually a misnomer, the overwhelming majority of cases arising from transformed lymphoid cells. The only malignant lymphoma of unequivocal true histiocytic or macrophage origin is malignant histiocytosis (histiocytic medullary reticulosis of Robb-Smith).[21] This is a diffuse proliferation of malignant histiocytes usually associated with hepatosplenomegaly and consumptive cytopenias.[49] The occasional cases of large cell lymphoma with histiocytic markers probably represent tumoral examples of this disease. The true histiocytic nature of the malignant cells in malignant histiocytosis is suggested by the observation of in vivo erythrophagocytosis.[49] Marker studies of histiocytes demonstrate receptors for complement, high content of acid hydrolases, phagocytosis of latex particles and sensitized erythrocytes and cytoplasmic muramidase.[1] Demonstration of the latter by immunoperoxidase on fixed tissue sections may be of considerable diagnostic help in difficult cases.[50] The histiocytic nature of the proliferation is also supported by the pattern of spread, with selective involvement of normal his-

tiocyte domains: the sinusoids of the lymph nodes, liver and spleen. The condition was previously almost always progressive and fatal but now may be responsive to combination chemotherapy. A histologically similar but benign condition has been described in association with viral syndromes, particularly in immunosuppressed children.[51] The histiocytosis X complex (eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease) is also characterized by histiocytic proliferation, but the histiocytes are morphologically benign. The so-called soft tissue histiocytomas and fibrous histiocytomas are mesenchymal neoplasms probably unrelated to the monocyte-macrophage complex.

Hodgkin's Disease

The nature of the neoplastic proliferation in Hodgkin's disease remains unsettled. The mixed inflammatory infiltrate of plasma cells, lymphocytes, histiocytes and eosinophils suggested a reactive process to early observers. The clinical course and response to radiotherapy, however, is that of a malignant neoplasm. The diagnostic cell of Hodgkin's disease, the Reed-Sternberg cell, appears to be the neoplastic element. The accompanying inflammatory infiltrate may be an integral part of the neoplasm or more likely a host response. The nature of the Reed-Sternberg cell and its variants is unsettled. Similar binucleate cells with prominent nuclei may be seen in reactive lymph node conditions, such as infectious mononucleosis, and have been considered transformed lymphocytes. The defect in cellular immunity and tendency for paracortical involvement in Hodgkin's disease was for many years considered evidence of T cell origin. Immunoperoxidase study of tissue from Hodgkin's disease has shown surface and intracellular immunoglobulin associated with Reed-Sternberg cells.[52] However, the immunoglobulin is polyclonal and evidence suggests it is passively taken up by the Reed-Sternberg cells and not synthesized by them.[53] Recently, two groups have succeeded in establishing Hodgkin cells in tissue culture.[54,55] The cells morphologically resemble Reed-Sternberg cells and exhibit cytologic and cytogenetic evidence of malignancy. The cultured cells lack surface immunoglobulin and do not form E rosettes, but have receptors for complement and the Fc portion of IgG and secrete muramidase. These are features of the monocyte-macrophage complex and suggest that the Reed-Sternberg cell may be histiocytic in origin. However, uncultured Reed-Sternberg cells in tissue sections do not demonstrate immunoperoxidase staining for muramidase, and it is difficult to unequivocally establish that the cells observed in culture were actually derived from Reed-Sternberg cells. Indeed, one of these cell lines has subsequently been shown to be of nonhuman origin.[56] Thus, although the results of these tissue culture studies are exciting, the nature of the cellular proliferation in Hodgkin's disease remains unsettled.

Conclusions

Analysis of cell surface markers has provided enormous insight into the ontogeny of the immune system and the nature of the neoplastic proliferations derived from them—the malignant lymphomas. The development of new marker systems, including the hybridoma-derived monoclonal antibodies, promises to extend greatly our ability to discriminate classes of normal and neoplastic lymphoid cells. In the future, application of cell surface marker studies to the study of the lymphomas should continue to advance our ability to diagnose, classify and manage these conditions.

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